

US-PAT-NO: 5625126

DOCUMENT-IDENTIFIER: US 5625126 A

TITLE: Transgenic non-human animals for producing heterologous antibodies

DATE-ISSUED: April 29, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lonberg; Nils	Redwood City	CA	N/A	N/A
Kay; Robert M.	San Francisco	CA	N/A	N/A

US-CL-CURRENT: 800/18, 536/23.1, 536/23.5, 536/23.53

CLAIMS:

What is claimed is:

1. A transgenic mouse containing in its genome a transgene comprising in operable linkage a plurality of human V genes, a plurality of human D genes, a plurality of human J genes, a human .mu. C.sub.H gene, at least two different non-.mu. human C.sub.H genes and associated isotype switching sequences, wherein human .mu. and human .gamma. switch sequences are located in closer proximity to each other than in the naturally occurring human immunoglobulin locus; and wherein in lymphocytes of said mouse the transgene undergoes productive VDJ rearrangement and .mu. to .gamma. isotype switching by recombination between the human .mu. and human .gamma. switch sequences such that the mouse produces a serum containing immunoglobulins of at least three human heavy chain isotypes in response to antigenic stimulation.
2. A transgenic mouse of claim 1, wherein the lymphocytes further have integrated a human light chain transgene.
3. A transgenic mouse of claim 2, wherein the serum comprises a population of IgG comprising a subpopulation of IgG composed of human .gamma.1 and human .kappa. and a subpopulation of IgG composed of human .gamma.3 and human .kappa..
4. The transgenic mouse of claim 1, wherein the human .gamma. switch sequences is contained within an approximately 5.3 kb HindIII fragment.
5. The transgenic mouse of claim 1, wherein the human .gamma. switch sequences is contained within an approximately 4 kb HindIII fragment.

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ABSTRACT:

The invention relates to transgenic non-human animals capable of producing heterologous antibodies and methods for producing human sequence antibodies which bind to human antigens with substantial affinity.

5 Claims, 110 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 89

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5625126

Detailed Description Text - DETX (692):

Our results demonstrate that these important cis-acting regulatory elements are either closely linked to individual .gamma. genes, or associated with the 3' heavy chain enhancer included in the HC1 and HC2 transgenes. Because the HC1 and HC2 inserts undergo transgene-autonomous class switching--which can serve as a marker for sequences that are likely to have been somatically mutated--we were able to easily find hypermutated transcripts that did not originate from translocations to the endogenous locus. We found somatically mutated .gamma. transcripts in three independent transgenic lines (two HC1 lines and one HC2 line). It is therefore unlikely that sequences flanking the integration sites of the transgene affect this process; instead, the transgene sequences are sufficient to direct somatic mutation.